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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/943,664	08/30/2001	David Botstein	P2548P1C8	2448

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EXAMINER	
O'HARA, EILEEN B	

ART UNIT	PAPER NUMBER
1646	

MAIL DATE	DELIVERY MODE
11/16/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	09/943,664	BOTSTEIN ET AL.	
	Examiner	Art Unit	
	Eileen B. O'Hara	1646	

-- *The MAILING DATE of this communication appears on the cover sheet with the correspondence address* --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *17 August 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☐ Claim(s) _____ is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☐ Claim(s) _____ is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 17 August 2007 has been entered.

Claims Status

2. Claims 27-34 are pending in the instant application. No claim was amended in the response filed 17 August 2007.

Claim Rejections - 35 USC §§ 101 and 112

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

3. Claims 27-34 remain rejected under 35 U.S.C. 101 because the claimed invention is not supported by either a specific and substantial asserted utility or a well established utility.

Claims 27-34 also remain rejected under 35 U.S.C. 112, first paragraph. Specifically, since the claimed invention is not supported by either a specific and substantial asserted utility or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention.

The basis for these rejections is set forth at pp. 3-7 of previous Office Action (Paper mailed March 24, 2003), at pp. 3-6 of Paper mailed Sept. 24, 2003, at pp. 3-14 of the Paper Mailed March 17, 2005, Paper mailed Sept. 20, 2005 at pages 3-8, Paper mailed January 24, 2005, pp. 1-8 of the paper mailed March 7, 2007, and below.

Applicant's arguments (pp. 5-12, Paper filed August 17, 2007) have been fully considered but are not found to be persuasive for the following reasons.

To review prosecution briefly, the Examiner has made a prima *facie case* that the mild amount of gene amplification (approximately 2 fold to 4 fold) of nucleic acids encoding the claimed protein are not indicative of an increased amount of mRNA or protein. It is noted that the data are drawn only to the comparison of genomic DNA. There is no disclosure of mRNA levels. Thus, the issue here is not whether the expression levels based upon DNA were significantly different in the tested tumors, but rather whether this data makes it more likely than not that the protein encoded by the gene is overexpressed.

Applicants on page 5 discuss patent 7,208,308, and assert that it has similar claims supported by the same utility based on similar data to that of the instant application. However, upon examination of the application, it is not clear that the utility requirement was considered specific and substantial because of amplification of genomic DNA, or because it was determined that the polypeptide was a serine protease, and therefore the protein had a specific and substantial utilty.

Applicants on pages 5-6 assert that a rejection for lack of utility is only proper when the asserted utility violates a scientific principle or is wholly inconsistent with contemporary knowledge in the art (MPEP § 2107.02 III B, citing *In re Gazave,* 379 F.2d 973 (CCPA 1967)). However, that section of the MPEP states:

> "Inventions asserted to have utility in the treatment of human or animal disorders are subject to the same legal requirements for utility as inventions in any other field of technology. In re Chilowsky, 229 F.2d 457, 461-2, 108 USPQ 321, 325 (CCPA 1956) ("There appears to be no basis in the statutes or decisions for requiring any more

conclusive evidence of operativeness in one type of case than another. The character and amount of evidence needed may vary, depending on whether the alleged operation described in the application appears to accord with or to contravene established scientific principles or to depend upon principles alleged but not generally recognized, but the degree of certainty as to the ultimate fact of operativeness or inoperativeness should be the same in all cases"); In re Gazave, 379 F.2d 973, 978, 154 USPQ 92, 96 (CCPA 1967) ("Thus, in the usual case where the mode of operation alleged can be readily understood and conforms to the known laws of physics and chemistry, operativeness is not questioned, and no further evidence is required."). As such, pharmacological or therapeutic inventions that provide any "immediate benefit to the public" satisfy 35 U.S.C. 101."

In the instant case, while the asserted utilty does not violate a scientific principle or is wholly inconsistent with contemporary knowledge in the art, the art teaches that it is not predictable that amplication of genomic DNA results in over-expression of mRNA.

On page 6 of the response, Applicants list 16 patents and assert that the PTO has acknowledged that on more than one occasion the asserted utility has been determined to be sufficient, and that the instant application relies on similar data. However, upon examination of those 16 applications, the data is not similar. In those 16 patents the asserted utility was based upon microarray data, which showed overexpression of mRNA in certain cancers, and in which is was determined that expression of mRNA correlates with expression of protein. However, the data in the instant application is amplification of genomic DNA, and as discussed in previous office actions it is not predictable that amplification of genomic DNA results in over-expression of mRNA.

First, there are several problems with the data provided in this example. Half of the colon cancer samples tested positive. Therefore, if a sample were taken from an individual with colon

cancer for diagnosis, it is as likely than not that this assay would yield a false negative result. Furthermore, the art recognizes that lung epithelium is at risk for cellular damage due to direct exposure to environmental pollutants and carcinogens, which result in aneuploidy **before** the epithelial cells turn cancerous. See Hittelman (2001, Ann. N. Y. Acad. Sci. 952:1-12), who teach that damaged, precancerous lung epithelium is often aneuploid. See especially p. 4, Figure 4. The gene amplification assay in the instant specification does not provide a comparison between the lung tumor samples and normal lung epithelium and does not correct for aneuploidy. Thus it is not clear that PRO341 is amplified in cancerous lung epithelium more than in damaged (non-cancerous) lung epithelium. One skilled in the art would not conclude that PRO347 is a diagnostic probe for lung cancer unless it is clear that PRO347 is amplified to a clearly greater extent in true lung tumor tissue relative to non-cancerous lung epithelium.

Second, even if the data had been corrected for aneuploidy and a proper control had been used, the data have no bearing on the utility of the claimed PRO347 *polypeptides*. In order for PRO347 polypeptides to be overexpressed in tumors, amplified genomic DNA would have to correlate with increased mRNA levels and increased polypeptide levels. No data regarding PRO347 mRNA or PRO347 polypeptide levels in lung tumors have been brought forth on the record. The art discloses that a correlation between genomic DNA levels and mRNA levels cannot be presumed, nor can any correlation between genomic DNA levels and polypeptide levels.

At pages 6-8 of the response, Applicants maintain that Orntoft, Pollack and Hyman demonstrate that gene amplification levels are more likely than not to correlate with mRNA levels, and submit three additional references, Lin et al., Imam et al. and Blancato et al., that

demonstrate that the art accepts that more often than not, which is the standard that must be satisfied for utility, there is good correlation between gene amplification and mRNA levels.

The Lin et al., Iman et al. and Blancato et al. references have been considered, but are not persuasive. EGF (Lin et al.) and thymidylate synthase (Imam et al.) and c-myc (Blancato et al.) all confer a selective advantage for growth for cancer cells, and Godbout (discussed in previous office actions) teaches that amplified genes are overexpressed if they provide a selective advantage. Additionally, there are references that teach that amplified genes do not correlate to mRNA and/or protein levels.

Applicants on page 9 of the response discuss the Godbout reference, and assert that Godbout does not teach that amplified genes are only overexpressed if they provide a selective advantage, and that Godbout simply states that "it is likely that a gene located ~ 400 kb from the MYCH gene will be consistently amplified as an intact unit unless its product provides a growth advantage to the cell", and thus, Godbout suggests that selective advantage may play a role in why a particular gene may be co-amplified with another gene. Applicants submit that this aspect of the Godbout teachings is not relevant to Applicants' assertion of utility, which is not based on any gene that is alleged to be co-amplified , and in addition, Godbout does not discuss whether there is a correlation between gene amplification and protein overexpression of a gene that is not co-amplified. Thus, Applicants maintain that Godbout does not teach that Applicants assertion of utility is wholly inconsistent with or violates any scientific principles nor does Godbout make it more likely than not that one of ordinary skill in the art would doubt Applicants' assertion of utility.

Applicants' arguments have been fully considered but are not deemed persuasive. Godbout et al. (1998, J. Biol. Chem. 273(33):21161-8) speak to general lack of correlation

between gene amplification and mRNA/protein overexpression. The abstract of Godbout teaches "The DEAD box gene, DDX1, is a putative RNA helicase that is co-amplified with MYCN in a subset of retinoblastoma (RB) and neuroblastoma (NB) tumors and cell lines. ***Although gene amplification usually involves hundreds to thousands of kilobase pairs of DNA, a number of studies suggest that co-amplified genes are only overexpressed if they provide a selective advantage to the cells in which they are amplified.***" (emphasis added). The protein encoded by the DDX gene *had been characterized* as being a putative RNA helicase, a type of enzyme that *would be expected to confer a selective advantage* to the cells in which it (the DDX gene) was amplified. On page 21167, right column, first full paragraph, Godbout et al. state ***"It is generally accepted that co-amplified genes are not over-expressed unless they provide a selective growth advantage to the cell*** (48, 49). For example, although ERBA is closely linked to ERBB2 in breast cancer and both genes are commonly amplified in these tumors, ERBA is not overexpressed (48). Similarly, three genes mapping to 12q13-14 (CDK4, SAS and MDM2) are overexpressed in a high percentage of malignant gliomas showing amplification of this chromosomal region, while other genes mapping to this region (GADD153, GL1, and A2MR) are rarely overexpressed in gene-amplified malignant gliomas (50, 51). The first three genes are probably the main targets of the amplification process, while the latter three genes are probably incidentally included in the amplicons." (emphasis added). There is no evidence in the instant application that PRO347 confers any growth advantage to a cell, and thus it cannot be presumed that the protein is overexpressed because the genomic DNA including the gene being studied gene is amplified.

Applicants on pages 9-10 discuss the Pennica reference (of record), and assert that WISP-

1 gene amplification and RNA expression levels showed a significant positive correlation, and that the RNA expression pattern of WISP-2 cannot be accurately attributed to gene amplification of WISP-2, this result should be disregarded. While the RNA expression pattern of WISP-2 may not be accurately attributed to gene amplification of WISP-2, another specific example is provided by Konopka et al. (Proc. Natl. Acad. Sci. (1986) 83:4049-4052), who state that "Protein expression is not related to amplification of the abl gene but to variation in the level of bcr-abl mRNA produced from a single Ph1 template" (see abstract).

An additional reference that provides evidence that gene amplification does not generally lead to increased transcript is Li et al. (2006, Oncogene, Vol. 25, pages 2628-2635). Li et al. used a functional approach that integrated simultaneous genomic and transcript microarray, proteomics, and tissue microarray analyses to directly identify putative oncogenes in lung adenocarcinoma. On page 2633, right column, Li et al. state: "***In our study, 68.8% of the genes showing over-representation in the genome did not show elevated transcript levels***, implying that at least some of these genes are 'passenger' genes that are concurrently amplified because of their location with respect to amplicons but *lack biological relevance in terms of the development of lung adenocarcinoma.*" Since more than half of the amplified genes were not overexpressed, Li et al. constitutes strong evidence that ***it is more likely than not that gene amplification does NOT correlate with increased protein levels***, absent evidence that the protein has biological relevance in cancer. There is no such evidene for PRO347.

Applicants submit that the evidence under consideration includes references relied on by the Office and references relied on by Applicants, and in addition Applicants rely on the 15 recently allowed patent applications that claim a polypeptide whose diagnostic utility is based on

demonstrated gene amplification in cancerous tissues, and that the totality of this evidence currently under consideration does not demonstrate that the asserted utility violates a scientific principle, nor is the totality of the evidence wholly inconsistent with contemporary knowledge in the art.

Applicants' arguments have been fully considered but are not deemed persuasive. The allowed patents are not relevant as discussed supra. The Office maintains it's position based on the cited art, as discussed in the previous office actions and in above. Accordingly, the Examiner maintains the conclusion that it is more likely than not that the PRO347 protein would *not* be expected to be found in increased amounts in the cells tested by applicants, and thus has no readily available utility as a cancer diagnostic.

Conclusion

4. No claim is allowed.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Eileen B. O'Hara, whose telephone number is (571) 272-0878. The examiner can normally be reached on Monday through Friday from 10:00 AM to 6:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Nickol can be reached at (571) 272-0835.

The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (571) 272-1600.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://portal.uspto.gov/external/portal/pair. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll free).

Eileen B. O'Hara, Ph.D.

Patent Examiner

EILEEN B. O'HARA
PRIMARY EXAMINER